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Genetic Moderators and Psychiatric Mediators of the link between Sexual Abuse and Alcohol Dependence

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Abstract

Background/Objective—This study used a case-control female sample to test psychiatric mediators and genetic moderators of the effect of sexual abuse on later alcohol dependence. The study also tested differences between alcohol dependent women with or without a history of sexual abuse on variables that might affect treatment planning.

Methods—A case-control design compared 192 treatment-seeking alcohol dependent women with 177 healthy population controls. All participants were assessed for alcohol-related behaviors, sexual abuse history, psychiatric problems, and personality functioning. Markers were genotyped in the CRHR1, MAO-A and OPRM1 genes.

Results—The association of sexual abuse with alcohol dependence was limited to the most severe category of sexual abuse involving anal or vaginal penetration. Of the five psychiatric disorders tested, anxiety, anorexia nervosa, and bulimia met criteria as potential mediators of the abuse-alcohol dependence association. Severe sexual abuse continued to have an independent effect on alcohol dependence status even after accounting for these potential mediators. None of the candidate genetic markers moderated the association between sexual abuse and alcohol dependence. Of alcohol dependent participants, those with a history of severe abuse rated higher on alcoholism severity, and psychiatric comorbidities.

Conclusion—Sexual abuse is associated with later alcohol problems directly as well as through its effect on psychiatric problems. Treatment-seeking alcohol dependent women with a history of abuse have distinct features as compared to other alcohol dependent women.

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Keywords

Sexual abuse; Psychiatric comorbidity; Genetics; Alcohol Dependence

1. Introduction

Clinical and population-based studies suggest that sexual abuse increases risk for later alcohol problems, including alcohol dependence, in women (see reviews Moncrieff and Farmer, 1998; Simpson and Miller, 2002). Abuse characteristics affect level of risk. Sexual abuse involving penetration and/or violence places women at the highest risk for subsequent alcohol problems (Bulik et al., 2001; Kendler et al., 2000; Molnar et al., 2001; Mullen et al., 1993). The effect of abuse on alcohol problems may also be more potent if the abuse occurs in childhood (Spak et al., 1998; Waldrop et al., 2007), although other evidence suggests similar problems in those only abused in adulthood (McCauley et al., 1997). Studies of childhood sexual abuse have also noted an early initiation of alcohol use in women with a history of abuse (Edgards, 2002; Kilpatrick et al., 2000; Sartor et al., 2007; Southwick Bensley et al., 1999), but not necessarily a faster progression from first drink to dependence (Sartor et al., 2007).

A number of explanations may account for this association: 1) sexual abuse may have an independent or direct effect on subsequent alcohol problems; 2) sexual abuse may increase risk for alcohol problems by increasing risk for conditions associated with alcohol problems (indirect effect); or 3) sexual abuse and alcohol problems may result from a common risk factor (spurious effect). Risk factors that might predict both sexual abuse and alcohol problems and thus account for a spurious association including genetic factors, parental psychopathology, parenting behavior, and family socioeconomic status have not fully accounted for the sexual abuse-alcohol problems association (Fergusson et al., 1996; Kendler et al., 2000; Luster and Small, 1997; Molnar et al., 2001; Mullen et al., 1993; Sartor et al., 2007).

It is unclear, however, whether the effect of sexual abuse is direct or mediated through conditions association with alcohol problems. The long-term effects of sexual abuse are not specific: Abuse increases risk for a range of psychiatric disorders including depressive disorders, bulimia nervosa, illicit drug problems, conduct problems, panic disorder, and social phobia (Dinwiddie et al., 2000; Kendler et al., 2000; Molnar et al., 2001). The association of sexual abuse with alcohol problems may be accounted for by an intermediary psychiatric condition. Tests of this indirect effect hypothesis provide some support for this hypothesis (Epstein et al., 1998; Kessler et al., 1997b), but these studies have typically focused on a single mediating disorder. One objective of this study is to test common psychiatric disorders as mediators of the sexual abuse-alcohol dependence association.

Not all sexually abused women, however, develop alcohol dependence. Risk may be moderated by individual characteristics including genetic vulnerability. Our second objective was to test multiple candidate genetic moderators of the sexual abuse-alcoholism association. Markers were chosen that have either displayed evidence of association with alcohol dependence (OPRM1 A118G) (Arias et al., 2006), or association with stress-related risk for alcohol problems (MAO-A promoter polymorphism (Ducci et al., 2007; Nilsson et al., 2008) and CRHR1 (Bradley et al., 2008; Blomeyer et al., 2008; Nelson et al., 2010)).

Little is known about how alcohol dependent women with a history of sexual abuse differ from those with no history of abuse. The evidence available suggests such women may present with more psychiatric symptoms, suicide attempts, legal problems, and family

problems than other alcohol dependent woman (Pirard et al., 2005; Schäfer et al., 2009). Identifying an abuse-specific profile of alcohol dependence would provide clinicians an opportunity to personalize treatment planning.

2. Methods

2.1. Participants

Between December 2003 and April 2007, all females seeking treatment for alcohol dependence at two Stockholm, Sweden outpatient clinics received brief information about the goals of this study and were asked if they could be contacted later for additional information (see figure 1). Prospective subjects were not excluded due to comorbid conditions. On second contact, both oral and written information was given to the women and informed consent was obtained. Healthy controls were recruited through the same two-stage process from women who attended routine gynecological health examinations in the area. Of those that did not agree to participate, the most common reasons given were being ill, having illness in the family, or lack of time. The recruitment structure and rates for cases and controls are presented Figure 1. All subjects were of self-reported Northern European ancestry. The study was carried out in accordance with the Declaration of Helsinki and approved by the Stockholm South Human Subjects Ethics Committee and the regional ethical review board.

All subjects were sober on the morning of the assessment day, as confirmed by a breathalyzer test, and were not in clinical withdrawal. For some assessments, some data were unavailable (e.g., forms miscoded). The actual number therefore varies slightly between the analyses.

2.1.2. Measures

Demographics: Subject characteristics (age, marital status, number of children, education level, and occupation) were obtained using a simple descriptive form. Education level was coded as: 0 = not completed primary school (grade, 1–9); 2 = completed primary school; 3 = completed secondary (high) school; 4 = college education, less than 3 years; and 5 = college education, more than 3 years. These characteristics were used as covariates where appropriate.

Sexual Abuse: All subjects completed an interview/questionnaire about history of sexual abuse adapted from the survey of sexual behavior in Sweden (Lewin et al., 1997). The interview asked about various forms of sexual contact from being forced to watch someone masturbate to forced anal or vaginal penetration. The current study focuses on three levels of sexual abuse: no reported sexual abuse, sexual abuse without anal or vaginal penetration, and sexual abuse with anal or vaginal penetration. Information was also collected on the age of first abuse, number of separate incidents and relationship to abuser.

Alcohol-related variables: Recent drinking was assessed using timeline follow-back (Sobell and Sobell, 1992). Severity of alcohol problems was estimated using the Alcohol Use Disorder Identification Test (AUDIT) (Babor et al., 1989; Saunders et al., 1993), originally developed as a screening test for hazardous drinking, but recently validated as a useful surrogate measure of severity (Donovan et al., 2006). The AUDIT is made up of 10 items, yielding a maximum score of 40. The instrument is divided into three domains: consumption, dependence, and alcohol-related problems. Consumption is reported in standard drinks originally defined as containing 12 g $\pm$ 10% of absolute alcohol. In the Swedish version of the AUDIT, definitions of a standard drink in the Swedish have been adapted to local consumption patterns as previously described (Göransson et al., 2003).

Family history of alcohol dependence in first-degree relatives was assessed using the family history questions from the Addiction Severity Index (McLellan et al., 1980). Non-alcoholic relatives were given a score of 0 and alcoholic relatives a score of 1. The total number of alcohol-dependent first-degree relatives was divided by the total number of first-degree relatives to obtain the measure of family history density. The Addiction Severity Index interviews also assessed age of onset for regular drinking and binge drinking.

Psychiatric status: Past and present diagnosis status for alcohol dependence and other psychiatric comorbidities was established through face-to-face the Structured Clinical Interview for DSM-IV diagnosis interviews (SCID) with all participants. Participants were assessed for a range of psychiatric diagnoses including alcohol abuse, alcohol dependence, illicit drug dependence, affective disorders, anxiety disorder, post-traumatic stress disorder, anorexia nervosa, and bulimia. The SCID has established excellent reliability and validity (First et al., 1997).

2.1.3. Genotyping—DNA was extracted using standard procedures from whole blood samples. Genotyping of all SNPs were completed using locus-specific primers, and fluorogenic allele-specific probes were obtained from ABI (Assays-on-Demand, identification No. C__2544843_10, C__11935968_10, and C__8950074_1). Approximately 10 ng of genomic DNA was amplified by real time-polymerase chain reaction (RT-PCR) using allele-specific probes. The reaction mixture consisted of 5 µl of master mix, 0.25 µl of 20× assay mix, and 10 ng of genomic DNA diluted in distilled water. Amplification was performed by RT-PCR (Gene Amp PCR system 7900; Applied Biosystems, Foster City, CA) using 384-well plates and the following amplification profile: 50°C for 2 minutes and 95°C for 10 minutes, followed by 40 cycles of 92°C and 60°C for 1 minute. After amplification, end-point fluorescence intensity was measured directly in the reaction plates (7900 sequence detector; Applied Biosystems). Four genotyping clusters were identified for each marker: two homozygous groups, heterozygotes, and no-DNA template controls.

The VNTR promoter MAO-A polymorphism was amplified using REExtract-N-Amp PCR ReadyMix (sigma). Primer sequences are described by (Sabol et al., 1998). The 30 bp variable number tandem repeat (VNTR) in the promoter region of the MAOA open reading frame were: forward, 5'-ACAGCCTGACCGTGGAGAAG-3' and reverse, 5'-GAACGTGACGCTCCATTCGGA-3'. The PCR reactions were performed on a Tetrad PTC-225 Thermo Cycler (MJ Research, Waltham, MA), at the following cycling conditions: initial denaturation at 94°C for 3 minutes, followed by 35 cycles of 94°C for 30 sec, 60°C for 30 sec and 72°C for 1 min, and a final extension at 72°C for 5 min. The PCR products that included five possible fragment sizes: 291, 321, 336, 351, and 381bp (corresponding to the 2-, 3-, 3.5, 4-, and 5-repeat alleles) were analyzed by electrophoresis on a 2% agarose gel.

Table 1 displays the four candidate genetic moderators. None of the markers deviated from Hardy-Weinberg equilibrium in controls or cases. The number of cases and controls successfully genotyped for each marker varied from 97% to 99% for cases and 98% to 100% for controls. Genotyping was completed blind to case-control status.

Mediation Analysis: Psychiatric disorders were tested as potential mediators of the sexual abuse-alcohol dependence association using a multistage logistic regression approach (Baron and Kenny, 1986; MacKinnon et al., 2002). Each disorder was considered a potential or candidate mediator as the study design does not allow us to clarify temporal order of psychiatric conditions and alcohol dependent status. To meet criteria as a potential mediator, five criteria had to be met: 1) Sexual abuse was associated with alcohol dependence (already

demonstrated); 2) Abuse was associated with the psychiatric disorder; 3) In models controlling for abuse status, psychiatric status was associated alcohol dependence; 4) In models controlling for abuse status, the association between abuse and alcohol dependence was either no longer statistically significant or it was attenuated; and 5) A statistically significant indirect path existed between abuse and alcohol dependence through the psychiatric disorder, as measured by the Sobel test (Sobel, 1982).

3. Results

Treatment-seeking alcohol dependent subjects were older (mean score $\pm$ standard error of mean: 45.1 ± 0.95 vs. 40.4 ± 1.1 , $p = 0.0003$), less likely to be married (percent (N): 33.5% (67) vs. 60.5% (114), $p < 0.0001$) and less educated (3.3 ± 0.07 vs. 4.1 ± 0.06 , $p < 0.0001$) but had more children (1.26 ± 0.08 vs. 0.88 ± 0.08 , $p = 0.001$) than healthy controls. Demographic variables were used as covariates in subsequent analyses as indicated.

Sexual abuse and Alcohol dependent status

Table 2 displays the rates of sexual abuse in the treatment-seeking alcohol dependent subjects and healthy controls. Sexual abuse was overrepresented in alcohol dependent subjects. This association was limited to the most severe category of sexual abuse involving anal or vaginal penetration; both cases and controls displayed similar rates of non-penetration sexual abuse. The association between abuse with penetration and alcohol dependence (as compared to those with no abuse or non-penetration abuse) was not attenuated by accounting for demographic covariates and family history of alcoholism, despite a strong independent association of family history with alcohol dependence risk (mean control score $\pm$ S.E.M.: 0.09 ± 0.03 vs. mean case score: 0.37 ± 0.03 , $p < 0.0001$). There was no evidence of an interaction between family history and abuse with penetration in predicting alcohol dependence status ($X^2(1) = 0.66$, $p = .42$; i.e., increased or decreased susceptibility in those with a positive family history of alcoholism).

Of those reporting any sexual abuse, 65.0% (N=67) reported an onset of sexual abuse in childhood (before age 18). Both child- and adult-onset abuse were associated with alcohol dependence and the strength of the association was similar for both groups (child-onset: OR= 3.89; 95%CI=2.14, 7.09; adult-onset: OR= 3.98; 95%CI=1.81, 8.76). Child-onset sexual abuse, however, was more common for those reporting non-penetration abuse only as compared to those reporting abuse with penetration (81.3% (N=26) vs. 56.5% (N=39), $X^2(1) = 5.83$, $p = 0.02$). There was no evidence of an interaction, however, between severity of sexual trauma and onset in terms of predicting dependence ($X^2(1) = 0.01$, $p = 0.98$).

3.1. Mediation by Psychiatric Disorders

Penetrating sexual abuse was associated with every psychiatric disorder (column 1 from table 3). Anxiety disorder status and both types of eating disorders continued to be associated with alcohol dependence after accounting for abuse status (column 2) and the Sobel test was significant in each of these cases suggesting a statistically significant indirect effect (column 4). In each case, abuse with penetration continued to be associated with alcohol dependence independently (column 3). There was no evidence of mediation by either affective disorders or PTSD.

3.2. Moderation by MAO-A, CRHR1, and OPRM1 Markers

Genetic moderators of the abuse-alcohol dependence association were tested in a series of logistic regression models. All models assumed additive genetic effects. After adjusting family-wise alpha levels for testing 4 markers, there was no evidence of either genetic main effects or of gene-environment interactions involving any of the markers (Table 4). Three

definitions of sexual abuse were tested: any abuse (results provided), penetrating abuse, and a three level variable from no abuse to non-penetrating abuse to abuse with penetration. Alternative abuse definitions resulted in similar results. Findings also did not differ if cases of sexual abuse were limited to those with an onset in childhood (available by request from the first author).

3.3. Profile of sexually-abused alcohol dependent subjects

The next series of analyses attempted to discriminate alcohol dependent women with a history of penetrating abuse from other alcohol dependent females (table 5 and 6). Alcohol dependent women with a history of penetrating abuse were younger, less educated and had fewer children. They were slightly less likely to be married or cohabitate, although this difference was not statistically significant (24.6% (N=15) vs. 38.2% (N=50), $p=0.06$). Alcohol dependent subjects with a history of penetration abuse were more impaired in terms of their current AUDIT score, reported an earlier onset of binge drinking. Only the elevated AUDIT scores, however, discriminated alcohol dependent subjects with a history of penetrating abuse after accounting for demographic variables. Three disorders were more common in alcohol dependent females with a severe sexual abuse history even after accounting for demographic covariates and AUDIT scores (table 6): anxiety disorders other than PTSD (most commonly panic disorder), PTSD, and dependence on other substances.

4. Discussion

Sexual abuse is one of the few risk factors that have established long-term effects into adulthood (Fergusson and Mullen, 1999). This study found women that reported a history of sexual abuse involving penetration were at risk for later alcohol dependence. Prior investigations have also suggested that severe sexual abuse involving violence or penetration may be associated with the highest levels of subsequent alcohol dependence (Bulik et al., 2001; Kendler et al., 2000; Molnar et al., 2001; Mullen et al., 1993). This was supported in the current analysis where treatment-seeking alcohol dependent women had had 10-fold higher odds of reporting a history of abuse with penetration as compared to controls. This increased risk was not dependent upon either a family history of alcohol dependence or early exposure to sexual abuse.

4.1. Limitations

Both cases and controls were recruited from urban clinics in a Northern European city and may differ in their alcohol use patterns or risk for sexual abuse from women from other racial or ethnic groups. As the cases were treatment-seeking, they likely display higher levels of impairment and psychiatric comorbidity than alcohol dependent women in the community. Despite these differences the association between sexual abuse and alcohol dependence has been identified in both community and clinical samples (Moncrieff and Farmer, 1998). It is unclear how treatment-seeking status may affect mediator and moderator analyses and these analyses must be retested in representative samples. As with many case-control studies, this study relied upon retrospective assessment of abuse status, alcohol behaviors, psychiatric problems and other variables. As such, subject reporting may be affected by forgetting or recall bias. Psychiatric mediators identified in our analyses should be considered candidate mediators until tested in a study using a prospective design. This limitation, however, does not extend to our moderation analyses where genotype status is assumed to be fixed.

4.2. Psychiatric Mediators

Anxiety and eating disorders did mediate a portion of this association, although in all cases sexual abuse continued to have a direct effect on alcohol dependence status. The anxiety

disorder finding is not surprising as anxiety disorders are one of the most prevalent comorbid mental disorders with alcohol dependence (Kessler et al., 1997a), and anxiety disorders frequently precede later alcohol disorders (Zimmermann et al., 2003). Similarly, alcohol dependence and eating disorders co-occur at high rates (Sinha and O'Malley, 2000). Although these findings require retesting in prospective studies that can clarify temporal association, abused women with anxiety or eating disorders may be a high risk subgroup and potential target for alcohol abuse prevention programs.

Perhaps the most likely candidate disorder and one previously implicated as a potential mediator (Epstein et al., 1998), however, did not mediate the association in this study. PTSD is an anxiety disorder and is distinct in being etiologically defined by exposure to a traumatic event. The current study found strong associations between both sexual abuse and PTSD and PTSD and alcohol dependence, but PTSD did not account for association between sexual abuse and alcohol dependence. Additional prospective studies will be necessary to clarify this pattern, but at least two points should be considered. First, only 21 individuals (or 5.3% of the total sample) met criteria for PTSD, whereas 101 individual reported some history of sexual abuse. It is unlikely that PTSD alone will account for the link between abuse and alcohol dependence, because it is uncommon even among those exposed to sexual abuse. Second, given these low rates of PTSD, it may be helpful to study whether subclinical levels of PTSD are informative in understanding the pathway to alcohol dependence.

4.3. Genetics Moderators

Identification of subgroups of individuals that are of greatest risk for later alcohol problems following sexual abuse exposure would allow targeted interventions. Of the three genes and four markers tested, however, none met statistical criteria as moderators. The marker displaying the strongest association was OPRM1 A118G which has previously displayed inconsistent association with alcohol dependence and other substance-related outcomes (Arias et al., 2006). In contrast, both CRHR1 and MAO-A markers had been implicated as moderators of association between sexual abuse and alcohol problems in prior studies (Ducci et al., 2007; Nelson et al., 2010; Nilsson et al., 2008). The null findings for the MAO-A VNTR may not be surprising. Ducci and colleagues (Ducci et al., 2007) found elevated rates of alcohol dependence in carriers of the low activity allele that had been exposed sexual abuse and no effect in those without a history of sexual abuse, but that is not a formal test of interaction. The test of the interaction itself did not meet statistical significance ($p=.09$). The study by Nilsson (Nilsson et al., 2008) with the same marker found increased risk of alcohol-related problems in females with a history of maltreatment if they carried the *high activity* (or 4-repeat) variant of the MAO-A, suggesting an opposite effect to that reported by Ducci and colleagues. Other studies of maltreatment-associated risk with this MAO-A marker have identified the low activity variant as the risk allele (Kim-Cohen et al., 2006). Finally, our findings for the CRHR1 markers contrast with the moderation effect observed by Elliott and colleagues (Nelson et al., 2010).

4.4. Profile of alcohol dependent subjects with a history of sexual abuse

Alcohol dependent subjects with a history of sexual abuse differed from other female alcoholics on demographic, alcohol-related, and psychiatric. It was not the case, however, that they differed on all indices. For alcohol-related variables, only severity of alcohol problems discriminated the groups after accounting for demographic covariates, while other alcohol-related differences were attenuated. Only anxiety disorders (particularly PTSD) and other substance disorders were elevated in alcohol dependent subjects with a history of abuse. The overall profile of increased alcohol problems and psychiatric and personality comorbidities suggests that alcohol dependent women with a history of sexual abuse

represent a distinct subgroup of treatment-seeking female alcoholics with complex presentation (Kang et al., 1999; Pirard et al., 2005; Schäfer et al., 2009), and likely unique treatment needs.

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Figure 1.
Flow chart of recruitment and sampling for case-control study of alcohol dependence in Swedish women.

Table 1

Genetic markers genotyped

Marker	Gene	Position	Function	Hapmap MAF	Control MAF	HWE p value	Case MAF	HWE p value
MAOA-LPR	MAOA	43249686	--	--	0.39	0.78	0.35	0.32
rs110402	CRHR1	41235818	intronic	0.45	0.48	0.19	0.46	0.29
rs1876831	CRHR1	41263526	intronic	0.195	0.16	0.06	0.14	0.72
rs1799971	OPRM1	154402490	missense	0.167	0.14	0.75	0.1	0.13

Table 2
Descriptive statistics and associations between sexual abuse and alcohol dependence

	History of Sexual Abuse			Group Comparisons		
	None	Non-penetration	Penetration	None vs. Non-penetration	None vs. Penetration	None or Non-penetration vs. Penetration
	% (N)	% (N)	% (N)	OR (95% CI) Unadjusted adjusted	OR (95% CI) Unadjusted adjusted	OR (95% CI) Unadjusted adjusted
Controls	86.4 (153)	9.0 (16)	4.5 (8)	1.3 (0.6, 2.78)	10.1 (4.7, 22.0) [§]	9.9 (4.9, 23.1) [§]
Alcohol dependent	59.9 (115)	8.3 (16)	31.8 (61)	1.4 (0.5, 3.4)	6.3 (2.7, 16.4) [§]	6.2 (2.6, 16.3) [§]

All adjusted tests controlled for age, marital status, education level, parenthood, and family history of alcoholism.

The overall test of differences between groups was highly significant, χ^2 (DF) = 45.56 (2), $p < 0.0001$.

[†] $P \leq 0.05$;

[‡] $P \leq 0.01$;

[§] $P \leq 0.0001$.

Table 3

Tests of psychiatric conditions as potential mediators of the association of penetration abuse with treatment-seeking alcohol dependence

	Controls	Cases	1. Abuse to mediator OR (95% CI)	2. Mediator to dependence OR (95% CI)	3. Abuse to dependence OR (95% CI)	4. Sobel test <i>P</i>
	%(N)	%(N)				
Candidate mediators						
Affective disorders	34.6 (65)	46.5 (93)	1.76 (1.0, 3.0) [†]	1.3 (0.8, 2.2)	7.3 (3.2, 18.4) [§]	0.36
Anxiety disorder	28.2 (53)	70.5 (141)	10.7 (5.2, 24.8) [§]	4.6 (2.6, 8.3) [§]	4.2 (1.8, 10.8) [‡]	0.0003
PTSD	1.0 (2)	9.5 (19)	14.5 (5.6, 42.2) [§]	1.4 (0.3, 10.0)	7.1 (3.0, 9.0) [§]	0.71
Anorexia Nervosa	4.9 (9)	16.0 (32)	3.1 (1.5, 6.2) [‡]	5.3 (2.1, 14.8) [‡]	7.2 (3.1, 18.7) [§]	0.02
Bulimia	9.0 (17)	32.0 (64)	3.7 (2.1, 6.5) [§]	5.0 (2.5, 10.6) [§]	6.0 (2.6, 15.7) [§]	0.002

All models adjusted for demographic covariates. Columns numbered 2 and 3 provide results from models in which both psychiatric status and abuse predicted case-control status. Due to sparse cells, it was not always possible to include an interaction term between abuse and psychiatric status in logistic regression models although no interaction terms tested were significant.

[†] $P \leq 0.05$;

[‡] $P \leq 0.01$;

[§] $P \leq 0.0001$.

Genotypic associations of variants in the Swedish women with a history of sexual abuse: Controls are compared to all alcohol dependent subjects

Table 4

marker	History of sexual abuse			No history of abuse			Main effect $\chi^2(\text{DF}), P$	Interaction $\chi^2(\text{DF}), P$
	Controls N (%)	Cases N (%)		Controls N (%)	Cases N (%)			
MAOA-LPR	3/3	1 (4.4)	6 (8.2)	24 (16.6)	12 (11.7)			
	3/4	13 (56.5)	33 (45.2)	69 (47.6)	53 (51.5)	0.46 (1), $P=0.50$	0.01 (1), $P=0.93$	
	4/4	9 (39.1)	34 (46.6)	52 (35.9)	38 (36.9)			
rs110402	T/T	7 (30.4)	16 (21.6)	35 (24.7)	32 (31.1)			
	C/T	11 (47.8)	43 (58.1)	79 (55.6)	54 (52.4)	1.23 (1), $P=0.27$	0.87 (1), $P=0.35$	
	C/C	5 (21.7)	15 (20.3)	28 (19.7)	17 (16.5)			
rs1876831	C/C	18 (78.3)	53 (73.6)	100 (69.4)	77 (74.8)			
	C/T	5 (21.7)	19 (26.4)	43 (29.9)	23 (22.3)	0.24 (1), $P=0.63$	0.37 (1), $P=0.54$	
	T/T	0 (0.0)	0 (0.0)	1 (0.70)	3 (2.91)			
rs1799971	A/A	20 (87.0)	56 (76.7)	107 (73.3)	88 (83.8)	4.60 (1), $P=0.03$	3.36 (1), $P=0.06$	
	A/G	3 (13.0)	17 (23.3)	36 (24.7)	17 (16.2)			
	G/G	0 (0.0)	0 (0.0)	3 (2.1)	0 (0.0)			

Blood samples were collected from 178 of 189 controls (94.1%) and 186 of 200 cases (93.0%). Minor variations in sample sizes across markers are attributable to marker call rates. All models included demographic covariates.

Table 5

Comparison of alcohol-dependent females with or without a history of abuse with penetration.

	History of Sexual Trauma		Unadjusted <i>p</i>	Adjusted for demographic variables <i>p</i>
	None or non- penetration (N=131) Mean (SD)	Penetration (N=61) Mean (SD)		
Demographic				
Age	46.98 (13.52)	41.87 (12.85)	0.01	--
Children	1.39 (1.23)	0.98 (1.12)	0.03	--
Education	3.41 (1.01)	3.05 (0.96)	0.02	--
Alcohol-related				
Audit	23.91 (7.02)	26.90 (7.42)	0.008	0.02
Age at regular drink *	26.19 (11.46)	23.10 (9.59)	0.07	0.79
Age at binge drink *	32.15 (13.96)	25.94 (11.34)	0.003	0.21
Family history density	0.34 (0.32)	0.42 (0.35)	0.09	0.17

* Regular drinking was defined as 2–3 drinking episodes per week and binge drinking was defined as typically imbibing 5 or more drinks at a drinking session.

Table 6

Comparison of alcohol-dependent females with or without a history of penetration abuse on psychiatric comorbidities.

	History of Sexual Trauma		Unadjusted comparisons	Comparisons adjusted for demographic variables and AUDIT scores
	None or non-penetration (N=131)	Penetration (N=61)		
	% (N)	% (N)	OR (95% CI)	OR (95% CI)
Psychiatric disorders				
Affective	47.3 (62)	45.9 (28)	0.9 (0.5, 1.7)	0.7 (0.4, 1.4)
Anxiety	63.4 (83)	86.9 (53)	3.8 (1.7, 8.7) [‡]	3.3 (1.4, 8.8) [‡]
PTSD	2.3 (3)	31.3 (13)	11.6 (3.2, 42.3) [§]	10.9 (3.1, 50.9) [‡]
Anorexia Nervosa	14.5 (19)	21.3 (13)	1.6 (0.7, 3.5)	1.0 (0.4, 2.5)
Bulimia	26.0 (34)	44.3 (27)	2.3 (1.2, 4.3) [‡]	1.6 (0.8, 3.3)
Other substance	16.2 (21)	37.7 (23)	3.1 (1.6, 6.3) [‡]	3.3 (1.4, 7.8) [‡]

[†] $P \leq 0.05$;

[‡] $P \leq 0.01$;

[§] $P \leq 0.0001$.